10:30 - 11:45

Predictive Stability for Biologics - The Discussion Continues

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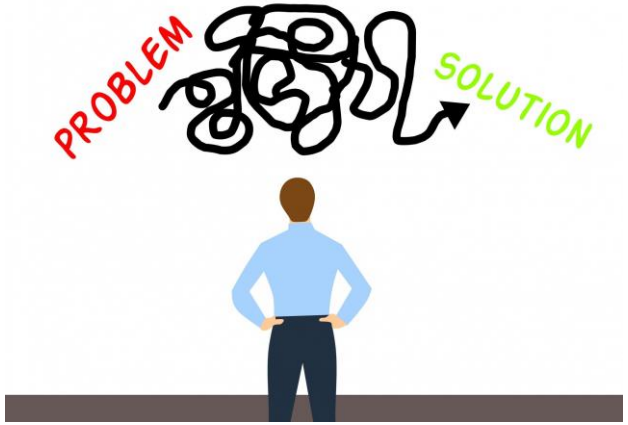
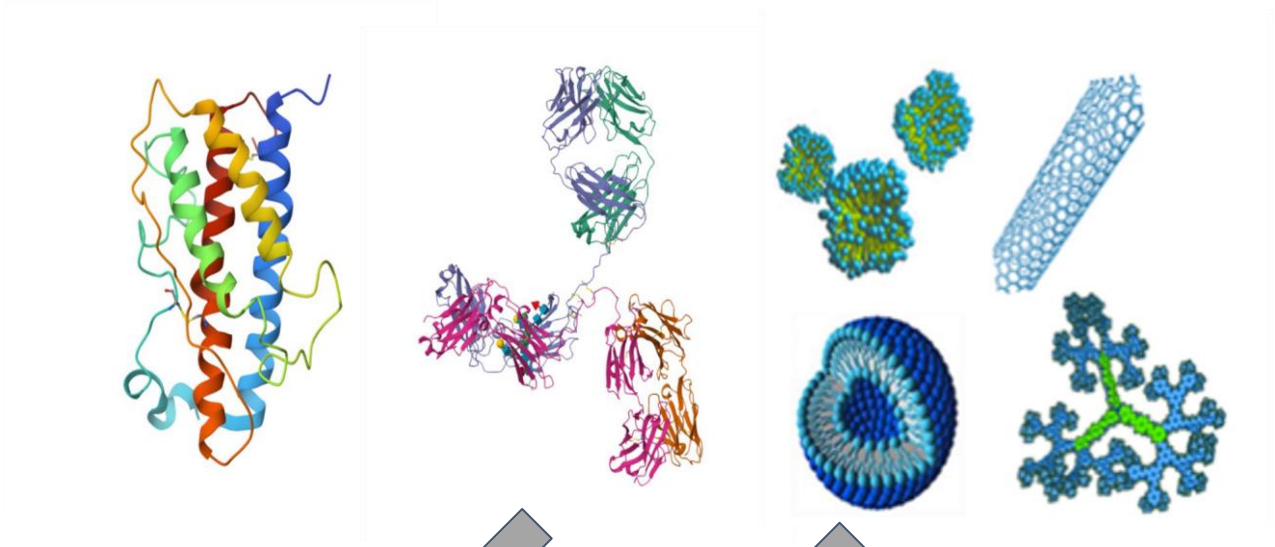
Predictive Stability - The Discussion Continues

Challenges in Shelf-life Setting for Biologics



- Desirable shelf-life based solely on primary stability batch data is typically years to enable global supply chains
- Analytical variability could lead to wide and inaccurate confidence intervals when using simple linear regression
- Complex degradation profiles (e.g., initial drop and then long-term, slow decrease)
- Degradation mechanism and shelf-life indicating parameters can be different between similar molecules
- Manufacturing changes and site changes during development or post approval- comparability and perceived differences
- Time (accelerated approval/unmet medical need) lead to reduced shelf-life due to limited real-time data at the time of submission

PATHWAY FOR PREDICTION OF A NEW PRODUCT



Prediction with Product-Specific Data

NEW DATA

MODELS

Approach may depend on specific CQA

MODELS

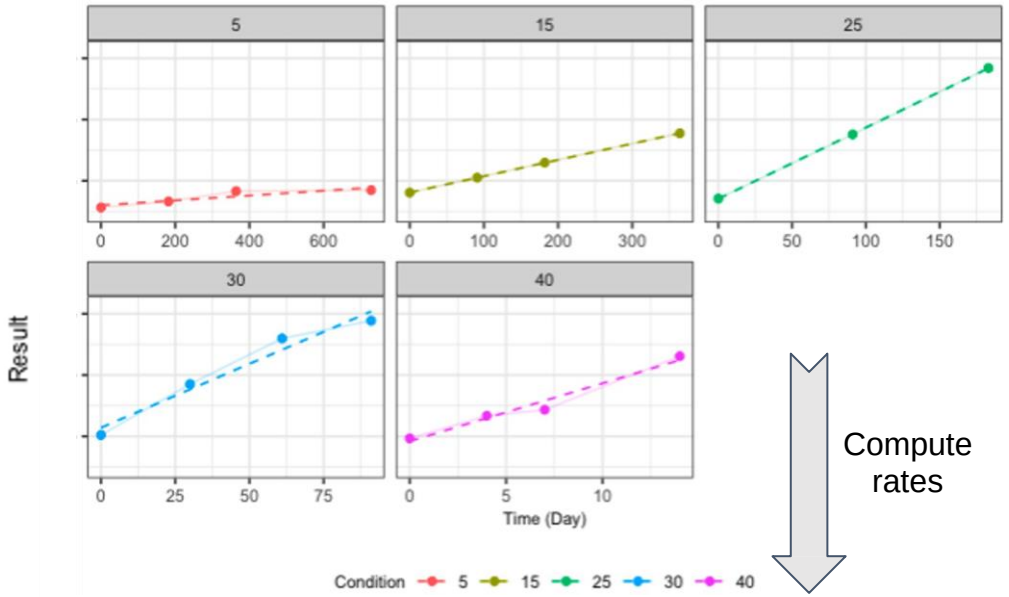
- Linear Arrhenius
- Advanced Kinetic Modeling (AKM)
- Bayesian
- ML/AI

Prediction from Prior Knowledge

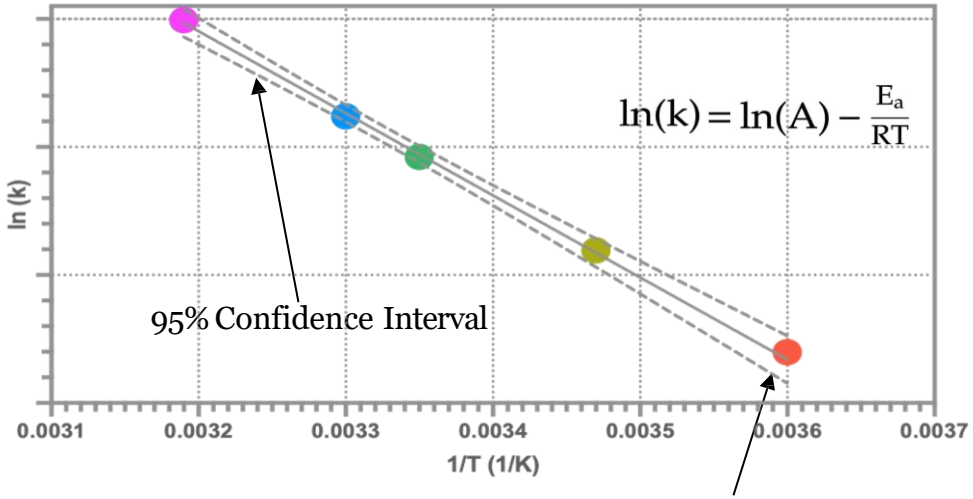
New DATA

LINEAR ARRHENIUS ANALYSIS PREDICTS ACIDIC DEGRADATION

Example: mAb acidic variants



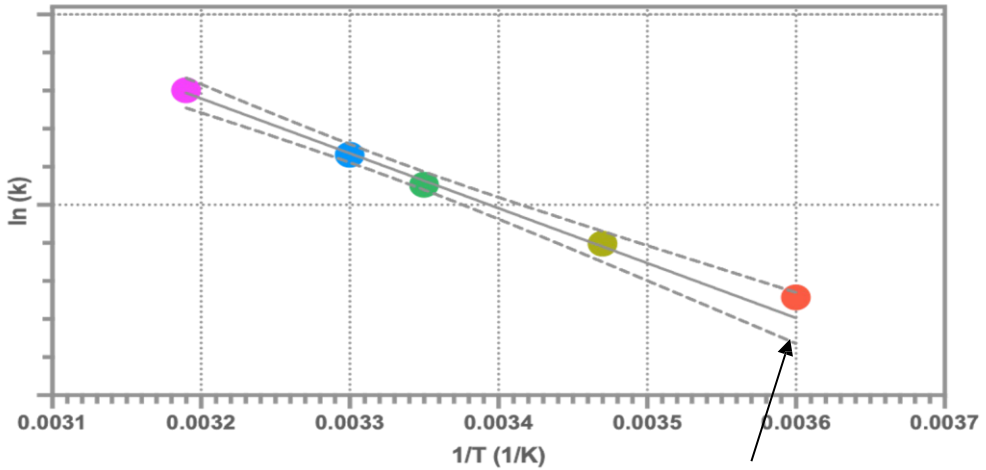
Compute rates



5°C Prediction

LINEAR ARRHENIUS IS NOT ALWAYS ACCURATE

Example: mAb HMWs



5°C Prediction

Not enough degradation

i. Sufficient degradation to determine accurate degradation rate
ii. Consider attribute stable enough not to be a concern

Non-linear behavior

i. Mechanistic changes between temps
ii. Different rate models across temps

ADVANCED KINETIC MODELING (AKM) CAN BE USED FOR COMPLEX DATA

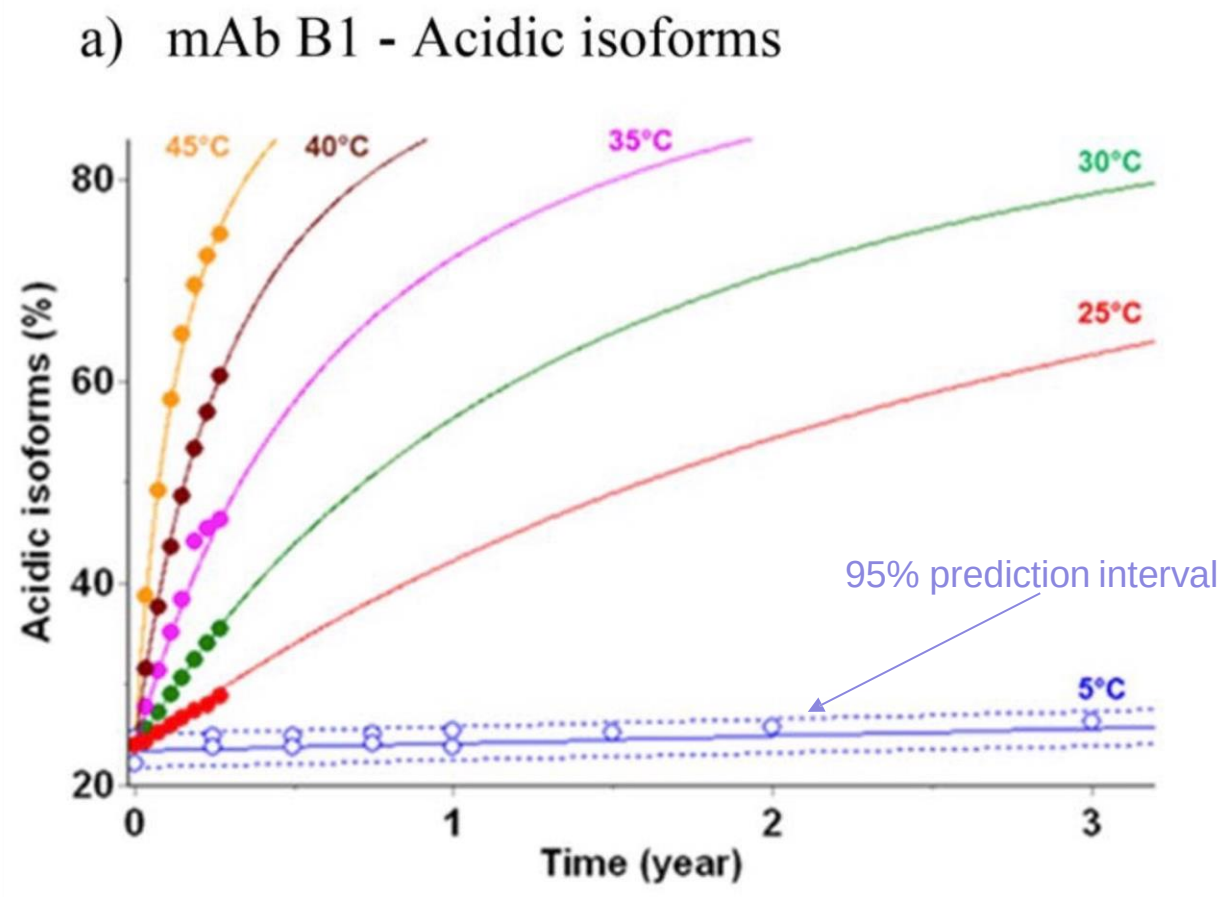
$$\frac{d\alpha}{dt} = k_1(1-\alpha)^{n_1}\alpha^{m_1} + k_2(1-\alpha)^{n_2}\alpha^{m_2}$$

α = reaction extent,

k_1, k_2 = reaction rates,

n_1, m_1, n_2, m_2 = reaction orders.

- Each reaction rate (k_1, k_2) is modeled using the Arrhenius equation.
- The reaction orders (n, m) might be treated as either fixed constants or parameters.



Huelsmeyer et al. Nature, Scientific Reports 13:10077(2023)

*Roduit, B.; Hartmann, M,; Folly, P.; Sarbach A.; Baltensperger, R. Prediction of thermal stability of materials by modified kinetic and model selection approaches based on limited amount of experimental points. Thermochim. Acta **579** 31-39 (2014).*

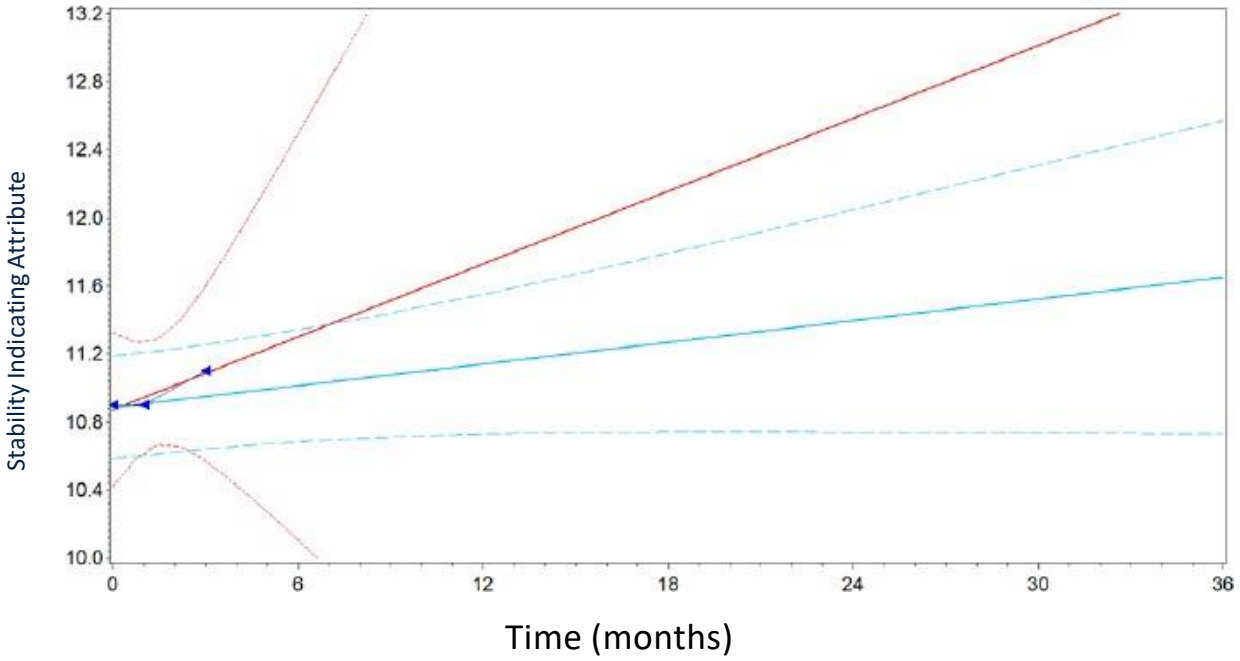
Bayesian Stability Example

Simple Ordinary Least Squares (OLS) prediction in red
Bayesian model prediction in blue

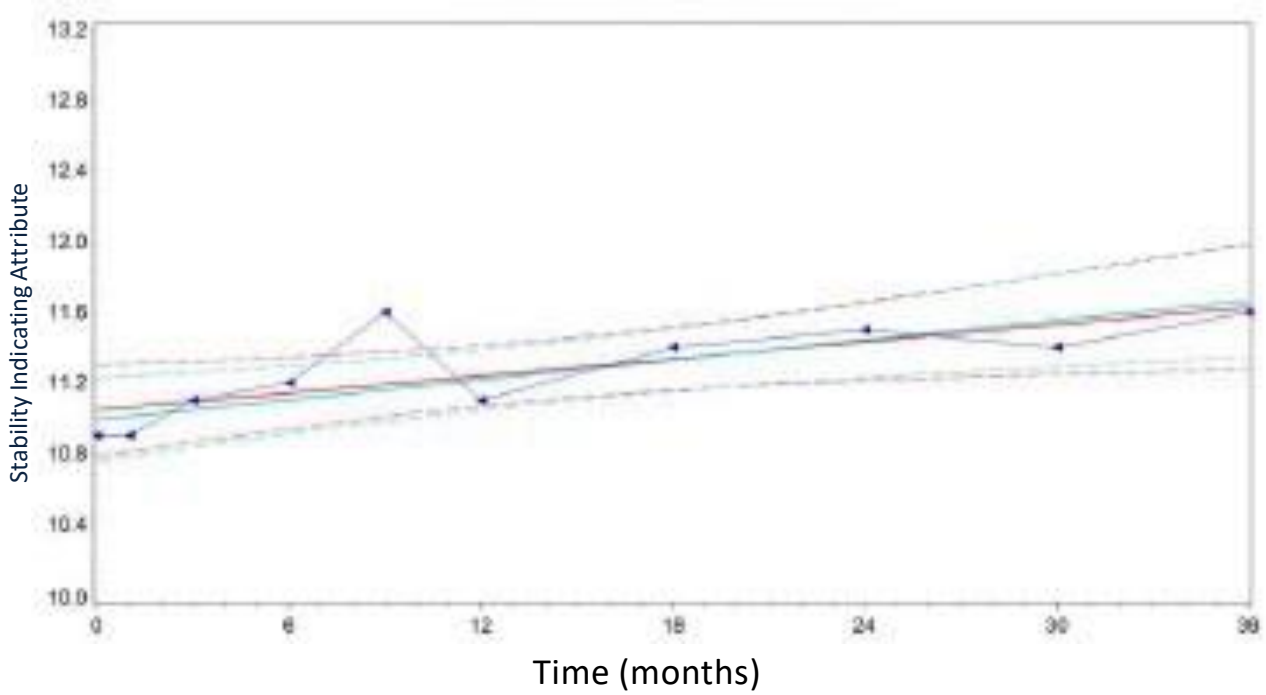
With associated confidence intervals for each

The example shown here contains graphs of the simple OLS and then the Bayesian model prediction using early data points and then real-time data verification to 36 months. Bayesian model is based on historical prior knowledge from over 20 real-time data sets.

1 and 3 months Real-time Data

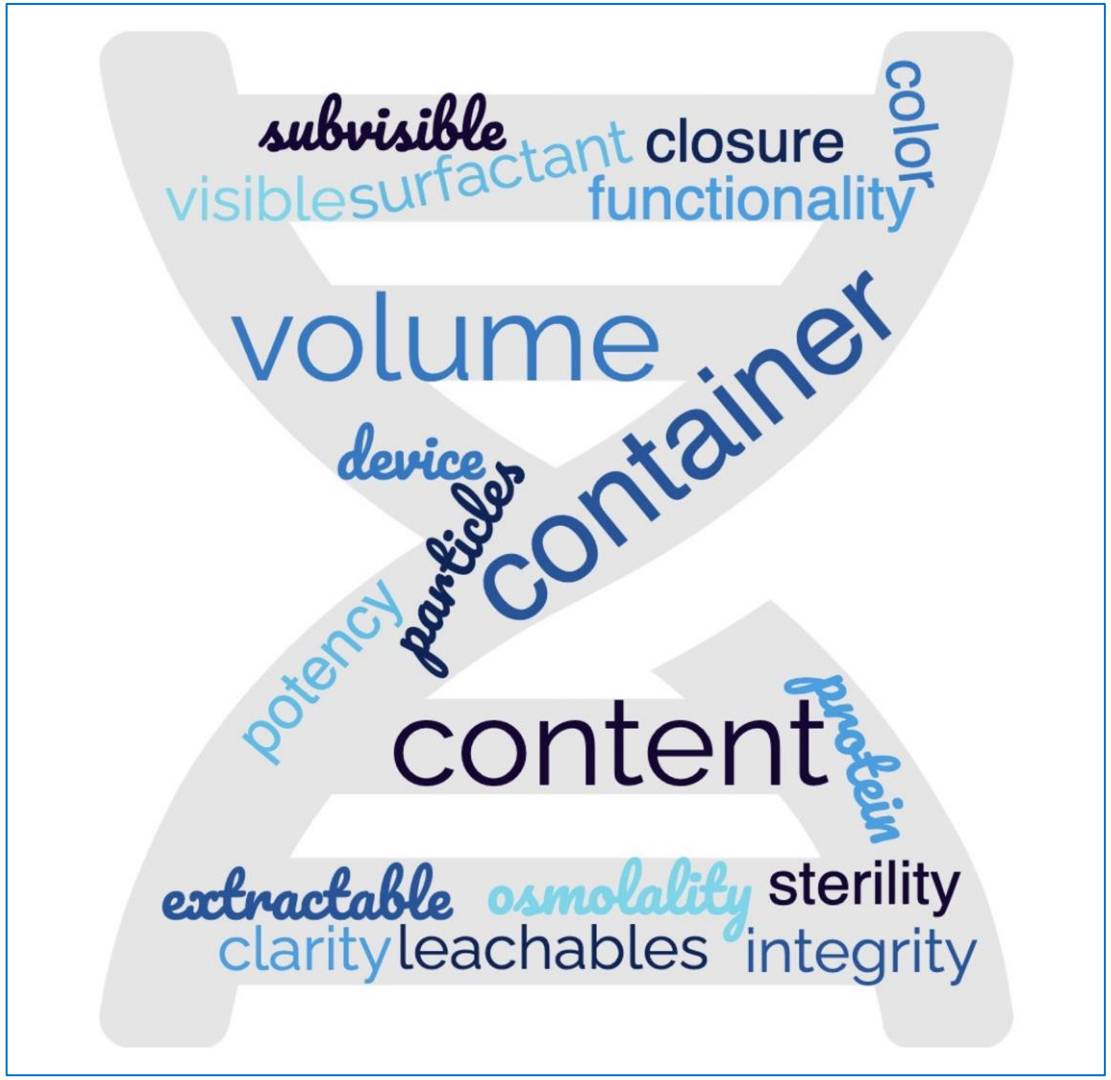


Up to 36 months Real-time Data



UNKNOWN UNKNOWNS

Many factors and attributes must be well-controlled to have confidence in a prediction.



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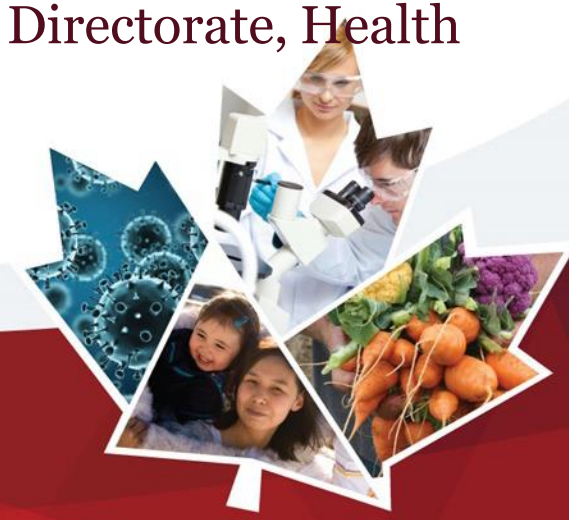
Predictive Stability : A Brief Regulatory Perspective

Paula Russell, PhD – Sr. Biologist/Evaluator, Biotherapeutics Quality Division, Biologic and Radiopharmaceutical Drugs Directorate, Health Canada



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Disclaimers

- The views expressed in this presentation are those of the presenter and do not convey official Health Canada policy

- The views expressed in this presentation are those of the presenter and are not intended to represent the ICH Q1/Q5C EWG

Why modeling within the stability space?

- Stability studies are routinely cited as a major rate-limiting step in biologic product development

- Support accelerated product development and shelf life setting in situations with seriously truncated development timelines

- Broader use in setting of specifications, temperature excursions, formulation, comparability assessments

Current landscape for stability modeling

- Generally, not an established practice for biologic products
  - Perception that it is difficult to model biologics owing to their complexity, structure/function relationship, and temperature response
  - ICH guidelines are not understood to facilitate the use of modeling, especially for biologics
- Regulatory - General and specific lack of familiarity with modeling
  - Types of models
  - Understanding of risk
- Recent approval/authorization of products where modeling was included
- Recent publications (*Huelsmeyer, 2023; Kuzman, 2021)*

Regulatory concerns

- Model is not suitable for the intended purpose
- Inaccurate predictions
- OOS results within predicted shelf-life
  - Significant regulatory implications
- OOS for parameter not included in the model
  - Fill volume/weight, particles (V and SV), appearance, protein content
- Appropriateness of the data included in the model
  - Justification needs to be provided and support the selection of input data
- Ongoing verification
- Component of a comprehensive stability program

Questions 1/3

1.What are the challenges to predict the stability behavior and set the shelf-life using stability modeling for biologics?

2. Which biologics are well suited for predictive stability approaches?

3.Which stability models are seen as most promising, and which ones need more experience/confidence?

Questions 2/3

4.What information and how much data would likely to be needed in the submission to support the stability model, and what are the critical components needed by regulators to begin to assess a model?

5.What is required to demonstrate a stability model is suitable for its intended purpose?

6.What strategies could be explored to help build regulatory understanding and confidence in predictive stability methodologies?

7.What is the benefit of using stability modeling to predict shelf-life compared to having a shelf-life extension protocol in a marketing application?

Questions 3/3

8.What type of verification data would be required if stability modeling is used to predict shelf-life?

9.What are the considerations around the application of product-specific and non-product-specific prior knowledge to predictive stability for shelf-life setting?

10.What are the risks of using predictive stability for shelf life setting and how can those risks be mitigated?

11.What are the specific risks and challenges to predicting retest/shelf-life for Biologics Drug Substances, typically stored frozen?

12.Is there a clear understanding between stability modeling and stability data extrapolation?

Mini Case Session 1 - Shelf Life Setting for Biologics:
Approaches and Challenges Including Stability Modeling Approaches and Advanced Statistical Designs

13:45 - 14:45 Wednesday, 24th January, 2024
Location Virginia Room